PERINATAL EFFECTS OF COCAINE AND AMPHETAMINE USE DURING PREGNANCY*

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BRIEF HISTORY OF COCAINE

COCAINE IS AN alkaloid derived from the leaves of the coca plant, indigenous to the Andes mountains of Peru and Bolivia. The euphorigenic properties of chewed coca leaf have been known to the Inca Indians for at least 5,000 years. Cocaine, however, did not reach Europe until brought by the Spaniards during the 16th century. Despite its importation, little interest was aroused in cocaine until popularized and promoted by Sigmund Freud as a cure for various maladies in his 1884 book *Über Coca*. In 1866 an American chemist, John Styth Pemberton, developed a patent medicine with reported powers for "all nervous affections;" when marketed as a soft drink, it was called Coca-Cola. Cocaine was subsequently removed from Coca-Cola in 1903 and the stimulant was replaced by caffeine, which it still contains today. Cocaine was also widely used as a topical anesthetic, promoted by physicians and pharmacists as part of their unregulated therapeutic armamentarium. In literature cocaine gained prominence through the character of Sherlock Holmes, whose case-solving brilliance was often attributed to the mind-expanding properties of cocaine, to which he was addicted.

Cocaine found its way to America first in 1880–1890 through the black stevedores of New Orleans and subsequently to the white underworld about 1895–1900. The first attempts at the control of cocaine came from the fear that blacks would "overstep their bounds" under the influence of cocaine and move into white society. Those in favor of such controls introduced and

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perpetuated the myth that cocaine would make blacks resistant to bullets and would foster violence, including sexual violence, against white women. This ethnic repression was similar to that used against the many Orientals addicted to opium in the mid- to late 19th century, and who were expanding their economic horizons and competing against white laborers in a society undergoing industrial and geographic expansion.

Early in the 20th century a backlash developed against cocaine due to the recognition of the drug's addicting properties, disenchantment with physicians' and pharmacists' uncontrolled use of patent medicines, and a racist attack on blacks, all leading to the Pure Food and Drug Act of 1906 and the Harrison Anti-Narcotics Act of 1914. In addition, the United States was becoming a world power participating in international commissions, beginning with the Shanghai Commission in 1909, which began to impose international controls against all drugs. A considerable "drug panic," much centered about cocaine, led a select committee that convened in New York to state "The problem of narcotic drug addiction has passed all bounds of reasonable comprehension in the State of New York and in the United States and has become the greatest evil with which the Commonwealth has to contend at the present time."[1] In 1910 President William Howard Taft echoed this feeling in a national statement, "The misuse of cocaine is undoubtedly an American habit, the most threatening of the drug habits that has ever appeared in this country."[2]

With the passage of the Harrison Act of 1914–1915, 46 of the then 48 states passed anticocaine legislation. From 1914 cocaine went underground, its use confined mainly to movie stars, jazz musicians, and wealthy thrill-seekers. Several reasons may help to explain why cocaine re-emerged with such a vengeance in the 1970s. An increasing segment of our American youth had grown up either using or exposed to drugs. During the 1960s, use of marijuana and other "soft" drugs made people casual about cocaine, which unfortunately had acquired the reputation of being a "soft drug"—nonaddicting, safe, and short-acting. Even in 1980, comprehensive textbooks of psychiatry continued to downplay the adverse effects of cocaine, claiming that chronic cocaine abuse did not appear to represent a medical problem. Cocaine was glamorized in films and rock music and became part of a large subculture. The dangers of amphetamine began to be recognized in the slogan "Speed kills," and many amphetamine addicts switched to a supposedly "safer" stimulant, cocaine. The pressure on importation of marijuana from Mexico and opium from the Far East led dealers to switch to cocaine. Between 1969–1974, cocaine confiscations increased sevenfold, but control of importation was difficult since the routes of supply were so varied.

Cocaine usage continued, mainly snorted by the middle and upper classes as a mild stimulant in social settings. In the 1980s, however, a new form of cocaine appeared on the streets of America with devastating potential for medical and social damage. This form of cocaine, called "crack" because of the popping or cracking sound made in its preparation, differed from other forms because it was cheap, easily prepared by the middle-line distributors, smokable, avoiding the use of needles, and highly addicting because of the intense euphorigenic properties of this new form of cocaine, leading to a deep posteuphoria crash. "Crack" smoking became firmly rooted in urban ghettos by 1985 and more recently spread rapidly across America. The prevalence of cocaine use in the United States reflects this growth, estimates of cocaine users increasing from 5.5 million users in 1974 to 21.6 million users in 1982 to 25 million users in 1985 to 35–40 million users in 1987. Recent government figures suggest that the number of drug users dropped by about 35% in 1989, but this was accompanied by an increase in hard-core chronic use during this same period.

To accommodate this increased demand during the 1980s, cocaine production in the Andes mountains of Peru and Bolivia, and to a smaller extent in Ecuador and Brazil, increased markedly. Raw cocaine is processed primarily in Colombia and distributed to Europe and to the United States, the latter mainly through Florida and the American Southwest. Despite our support of Colombian antidrug activities and a heavy emphasis on interdiction of cocaine at our borders, it is generally acknowledged that increasing amounts of cocaine are reaching our country.

Major Societal Impact of the Epidemic of Cocaine Use

The cocaine epidemic has touched almost every aspect of American lives and represents the major societal concern of the American people, outranking such concerns as Central America, terrorism, and arms control. Among the effects of the cocaine epidemic are:

Increase in crime. In New York City, for example, murders increased by 10.4% from 1987 to 1988, and "crack" was reportedly responsible for 38% of the 1,867 murders during 1989.[3] In Washington, D.C., 59% of men arrested tested positive for cocaine.[4] In other areas of our country 80% of men arrested tested positive for cocaine; almost half of all criminal trials in federal courts now involve narcotics prosecutions.[5] In addition, the number of injuries, shootings, knifings, and overdoses has dramatically increased, flooding our emergency rooms and hospital wards with victims of the drug epidemic. It is also estimated that emergency room admissions have increased 10 fold

between 1985 and 1987, largely due to the "crack" explosion.[6] Although most drug-related violence occurs within the ghettos—drug family versus drug family over turf and money—an increasing number of Americans are becoming personally affected by this tragedy.

Prison overcrowding. In response to an increasingly frustrated and punitive public mood, more jails and prisons are being built to incarcerate the increased number of drug-related convicted felons. In New York City the jailed population has risen from 10,000 in 1985 to about 18,000 in 1989.[3] Since 1983 New York State has spent $900 million to build 18,000 jail cells, and needs 9,000 more immediately. California has 81,000 people jailed, has built 21,000 prison cells since 1983, and plans 16,000 more at a cost of 3.2 billion dollars.[4]

Sexually transmitted diseases. AIDS continues to pose a growing threat to this population. By 1988 1,346 cases of pediatric AIDS had been reported,[7] with many more cases projected to occur. Seventy-eight percent of these cases were perinatally acquired: 53% from an intravenous drug abuser, 17% from a mother who was a sex partner of an intravenous drug user, and 7% from a mother having sex with another man at high risk. In New York State an anonymous HIV seroprevalence study in the late 1980s revealed that 0.16% of the babies were HIV positive.[8] In New York City 1.25% of all babies were HIV positive. AIDS is currently the ninth leading cause of death among one–four-year-old children and seventh in the 15-24-year-old group. It is expected that AIDS will enter the top five causes of death in one–four year olds by the year 1992.[9] AIDS takes a disproportionately heavy toll among minority groups.[10] Although blacks make up 15% of our population, 53% of the AIDS children are black. Hispanics make up 10% of our population but 22% of the AIDS children. It is estimated that by 1991 one out of every 10 pediatric hospital beds will be occupied by a child with AIDS.

In addition to the devastating impact on rates of HIV infection, cases of primary and secondary syphilis have increased steadily. From a low point in 1956 of 6,392 cases, the Centers for Disease Control reported 27,283 cases in 1986 and 40,275 cases in 1988.[7] This had led, of course, to marked increases in congenital syphilis across the country.

Child abuse and neglect. The number of cases of child abuse or neglect in New York City tripled between 1986 and 1988, now totalling more than 66,000 cases reported to the Bureau for Special Services for Children.[11] This has led to an increase in babies boarding in neonatal intensive care units and hospital wards and overcrowding of foster care facilities. The number of children in foster care has increased from about 20,000 in 1984 to almost

40,000 in 1989.[11] It is also known that 48%, nearly half, of infants under two years of age in "boarder" status, are placed there because of maternal drug use. In addition, families are destroyed as children themselves become actively involved in the drug trade.[12]

Impact on hospital costs. The total cost to our health care system has not been calculated. Florida estimates that the cost of getting the cohort of 17,500 cocaine-exposed babies born in 1987 out of the nurseries and intensive care units through special education and intervention programs into kindergarten is estimated to be $700 million.[6] A Los Angeles hospital reported that the cost of caring for a drug-exposed newborn infant in a neonatal intensive care unit ranges from $750 per day for a mild case to $1,768 per day in a severe case.[13]

Societal costs. Cocaine trade is estimated to be a $150 billion industry in the United States. The cost to society—legal, health, legislative, criminal, etc.—has been estimated to be $300 billion.[14] In addition, a future generation of workers, primarily unskilled and semi-skilled, has been eroded, causing great concern to our industries. Finally, work-related absenteeism and accidents have spiraled upward under the influence of increased drug and alcohol use.[15]

Impact on mothers and babies. One unfortunate aspect of this recent cocaine epidemic is the large increase in women using cocaine, a sex-related phenomenon not seen since the heavy involvement of women in morphine addiction during the mid-19th century. It is now estimated that as many as 30–40% of cocaine addicts are women, many of whom are in the childbearing age.

As a result, the number of babies reportedly exposed to drugs in New York City rose from 7.9 per 1,000 births in 1983 to 20.3 per 1,000 births in 1987; more than 5,000 drug-exposed babies were born in New York City in 1989.[11] Some hospitals in black urban ghetto areas report that 20–30% of all newborn infants test positive for illegal drugs in their urine, 80–90% being cocaine.[16] At one Brooklyn hospital 14% of all infants are cocaine positive, of whom 15% are also VDRL positive.[16] Other cities, such as Dallas, Denver, Oakland, Philadelphia, and Houston, all report three–four fold increases in drug-exposed infants between 1985 and 1988. In Florida 17,500 babies were born with positive urine toxicology screens in 1987.[17] Although precisely accurate figures are difficult to establish, it is estimated that about 11%, or 375,000 babies, are now born in the United States following intrauterine exposure to drugs.[18]

PHYSIOLOGY AND PHARMACOLOGY

Cocaine (benzoylmethylecgonine hydrochloride) is an alkaloid derived from the leaves of coca plants, most prominently *Erythroxylon coca*. The first extraction process yields a coca paste, a raw and generally impure product consumed primarily in South America. Further extraction with hydrochloric acid yields cocaine hydrochloride, which is usually diluted and either snorted or used intravenously. If the hydrochloride salt is treated with a base such as sodium bicarbonate and then reextracted with a solvent such as ether, the free base form, also called "crack" is produced.[19]

Cocaine displays varied pharmacokinetics based on its specific preparation and route of administration. Because cocaine is a very potent vasoconstrictor, it retards its own absorption when applied to mucous membranes, such as the nasal mucosa when snorted or gastrointestinal mucosa when ingested. This vasoconstriction leads to slower achievement of peak levels of cocaine in the blood and brain. Cocaine plasma levels peak in about 15 to 60 minutes following snorting and in about 45 to 90 minutes after ingestion.[19] Peak levels of cocaine are reached much more rapidly following smoking or intravenous use. This more rapid absorption causes an intense euphoria and severe posteuphoria "crash" that reportedly leads to an intense craving and potentially rapid development of dependence on the drug.

Once absorbed, cocaine crosses mucous membranes easily and may accumulate in the brain. Cocaine is metabolized by serum and hepatic cholinesterares to water-soluble inactive compounds, primarily benzoylecgonine and ecgonine methyl ester.[19] Cocaine may be detectable in blood or urine for less than 12 hours but its water-soluble products may be recovered from urine for up to one week, depending on the sensitivity of testing methodology. Usual toxicologic testing involves the use of either an enzyme-multiplied immunoassay technique (EMIT) or radial immunodiffusion, with confirmation by either gas chromatography or high performance liquid chromatography.

PERINATAL COMPLICATIONS

Obstetric. Recent articles document that cocaine use during pregnancy increases the risk of poor perinatal outcome. Perinatal complications may be divided into two major groups: adverse effects due to the life style frequently associated with maternal cocaine use and adverse effects due to the cocaine

itself. Life style issues related to cocaine use that impact negatively on perinatal outcome include poverty, homelessness, lack of prenatal care, poor nutrition, increase in sexually transmitted diseases, polysubstance abuse including alcohol, and increased incidences of such conditions as pneumonia, phlebitis, septicemia, hepatitis, endocarditis, meningitis, and convulsions, among others. In addition, other specific conditions linked to cocaine use pose serious threats to the mother and fetus.

Increase in early pregnancy loss. Chasnoff et al. found increased early pregnancy loss in previous pregnancies of cocaine-using women, but this retrospective analysis did not permit assessment of specific drug-taking patterns related to these early losses.[20] In other studies Hadeed and Siegel found a 3.5 fold increase in spontaneous abortions[21] and Bingol et al. found an increased stillbirth rate in cocaine-exposed pregnancies.[22] These losses are thought to be caused by cocaine-induced vasoconstriction of uteroplacental vessels with subsequent anoxic death of the fetus.

Abruptio placentae. A number of studies document an increased rate of abruptio placentae associated with cocaine use during pregnancy.[20,21,23] Although the mechanism for the premature placental separation is not established, cocaine blocks reuptake of catecholamines at adrenergic nerve endings. Increased levels of catecholamines increase cardiac rate, body temperature, and blood pressure,[19] all of which may play an etiologic role in causation of abruptio placentae.

Preterm delivery. The impact of maternal cocaine use on length of gestation is not clear. An early paper by Chasnoff et al.[20] found no increased prematurity, but a later report by his group did find a ninefold increase in preterm births after cocaine use.[23] In a small number of cocaine users, Hadeed found no increase in prematurity;[21] this was supported by a larger study by Zuckerman et al.[24] In contrast, however, data from both Chouteau et al.[25] and Cherukuri et al.[26] indicate significantly increased rates of prematurity following maternal cocaine use.

Low birth weight. Aside from Chasnoff's original 1985 report[20] in which he found no difference in birth weights between cocaine-exposed and control infants, a consensus has developed that cocaine use during pregnancy does retard fetal growth. Chasnoff's later paper did find a decrease in mean birth weight and an increase in low birth weight and intrauterine growth retardation when cocaine was used during the entire pregnancy.[23] Chouteau found a mean birth weight of 2,786 grams in cocaine-exposed newborns, with almost one third weighing less than 2,500 grams.[25] Fulroth noted an increase in intauterine growth retardation,[27] Cherukriri found a decrease in birth weight

and increase in intrauterine growth retardation,[26] Hadeed found a decrease in birth weight and increase in intrauterine growth retardation,[21] and Zuckerman reported a decrease in birth weight.[24] Although the mechanism for reduced fetal growth is not established, it is generally assumed to be mediated through reduced fetal nutritional support due to cocaine-mediated uteroplacental vasoconstriction.

Fetal head growth. Although Chasnoff originally reported no decrease in head circumference in cocaine-exposed newborns compared to controls,[20] his subsequent data did reveal such a decrease if cocaine was used throughout the pregnancy.[23] Decreases in neonatal head circumference in cocaine-exposed newborns have been confirmed by Hadeed,[21] Zuckerman,[24] Cherukuri,[26] and Fulroth.[27] These various data sets suggest, therefore, that maternal cocaine use is associated with a symmetric growth retardation in offspring, with reductions in both birth weight and head circumference. This pattern appears to be similar to that described in opiate-exposed newborns by Doberczak and Kandall,[28] although the mechanism in the latter case appears due to reduced organ cell number.

Congenital malformations. Although data in mice suggest that cocaine has major teratogenetic potential, data from human studies are contradictory. A number of studies have found that the genito-urinary system may have specific teratogenic vulnerability.[23 29,30] Bingol et al. reported that cardiac and skull defects were found more commonly in cocaine-exposed neonates.[22] On the other hand, other studies have failed to note an increased malformation rate in cocaine-exposed neonates.[21,24,31]

Fetal distress. The available literature does not note an increased incidence of cocaine-associated fetal distress, based on fetal heart tracings, meconium staining of amniotic fluid, or Apgar scores.

NEONATAL COMPLICATIONS

Cocaine-associated neurotoxicity during the newborn period has been clarified through recent publications. An original report by Madden described no obvious neurotoxicity in a series of eight cocaine-exposed newborns.[31] Subsequently Chasnoff described an encephalopathic syndrome of tremulousness and irritability associated with depressed interactive behavior and labile state control in cocaine-exposed neonates.[20] Subsequent work by Chasnoff confirmed neurobehavioral abnormalities in orientation, motor abililty, state regulation, and abnormal reflexes.[23] Cherukuri found abnormal neurobehavioral signs, including tremulousness, irritability, and muscular hypertonia in 38% of "crack"-exposed neonates.[26] Doberczak and Kandall

confirmed the presence of hypertonia, brisk tendon reflexes, irritability, and tremors in 34 of 39 cocaine-exposed babies.[32] In those 34 infants neurologic abnormalities were transient, lasting only a few days, and did not require specific treatment. No correlation could be found between neurotoxicity and specific perinatal variables such as route or quantity of maternal cocaine administration, gestational age, or birth weight. It is now apparent that neonatal cocaine neurotoxicity differs quite markedly from the abstinence associated with maternal opiate use. Opiate withdrawal presents in dramatic fashion in the newborn period with central nervous system, autonomic, respiratory, and gastrointestinal signs. This abstinence is associated with significant morbidity and even mortality if the opiate abstinence is not recognized and treated promptly. On the other hand, cocaine exposure causes a direct neurotoxicity manifest by neurobehavioral dysfunction which may range from subtle to striking. These neurobehavioral disturbances may be transient, and usually do not require treatment. Cocaine, however, may produce long-term neurodysfunction, which is now becoming apparent as the first cohort of "crack babies" enters nursery school.

In addition to neurobehavioral abnormalities, Doberczak and Kandall studied serial electroencephalographic tracings in cocaine-exposed neonates.[32] Electroencephalograms were abnormal in 17 of 38 infants during the first week of life, characterized as showing cerebral irritation with bursts of sharp waves and spikes and features of discontinuity. These abnormalities were unpredictable and did not correlate with variables related to maternal drug use, neonatal characteristics, or severity of neurologic dysfunction. In that study the authors demonstrated that all abnormal electroencephalograms reverted to normal when followed over a 3-to-12-month period, but the longer term impact of these changes is not known. Despite these abnormalities, no clinical seizures were observed during a seven-to-10 day observation period. Other workers have similarly noted the absence of clinical seizures in cocaine-exposed neonates. Chasnoff did note seizures, however, in six of 52 infants born to mothers after cocaine use throughout the pregnancy; two of those six infants were reported to have abnormal electroencephalograms.[23]

In addition to clinical encephalopathic and electroencephalographic changes, a study of echoencephalographic abnormalities in stimulant-exposed neonates has been recently published by Dixon and Bejar.[33] This study assesses a mixed exposure to cocaine and methamphetamine, however, in addition to some opiates. In this drug-exposed group, 35% of the neonates had abnormal ECHO studies, with the highest incidence in the stimulant (cocaine-methamphetamine) subgroup. Lesions suggestive of prior hemor-

rhagic or ischemic injury with cavitation, located anterior and inferior to the lateral ventricles, in the frontal lobes and basal ganglia, were found in 8% of the infants. Intraventricular hemorrhage was found in 12% of those drug-exposed babies, subependymal hemorrhage in 11% and subarachnoid hemorrhage in 14%. In addition, ventricular dilatation suggesting diffuse atrophy was seen in 10% of the study infants. Finally, cerebral infarction was evident in two of the cocaine-exposed infants. Despite these impressive ECHO studies, infants with abnormal findings did not display identifiable neurobehavioral abnormalities during the newborn period. This is not totally surprising since the location of the lesions may indicate damage which would be detectable when the infant is older and challenged with more complicated visual-motor and cognitive tasks.

Cerebral infarctions similar to those noted on ECHO studies cited above have been noted anecdotally in other reports in a small number of cocaine-exposed infants.[24,34] These cerebral insults are probably caused by cocaine-induced vasoconstriction leading to hypoxia and/or acute hypertension.

More focused studies of the impact of cocaine on newborn infants have recently been reported. One such study by Shih assessed auditory brain stem response in 18 cocaine-exposed babies.[35] Prolonged interpeak latencies were found, reflecting neurologic dysfunction at the level of the cochlear nucleus or higher.

Breastfeeding. Breastfeeding should be discouraged in cocaine-using women. Since cocaine is highly lipophilic, it passes readily into breast milk. Chasnoff reported one case of cocaine intoxication in a breast-fed infant whose mother used cocaine both topically on her gums and intranasally.[36] The infant developed neurotoxicity, including irritability, hyperactive reflexes, tremulousness, and mood lability. Chaney et al. reported seizures in an 11-day-old breast-fed infant whose mother applied topical cocaine powder to her nipples for relief of soreness.[37] It is also important to remember that a significant percentage of drug-using patients may be HIV-positive. Until the role of breast feeding in HIV transmission is clarified, this concern forms another reason for discouraging breastfeeding in cocaine-using women.

FOLLOW-UP STUDIES

Sudden Infant Death Syndrome (SIDS). The risk of SIDS in cocaine-exposed infants is not known. Chasnoff[20] has suggested that the risk may be high, although his data base was very small. Subsequently Chasnoff reported that 15% of 66 infants exposed to cocaine in utero subsequently died of SIDS. In support of this alleged association, Chasnoff studied cardiorespiratory

patterns in 32 cocaine-exposed infants at eight to 14 days of age.[38] Pneumograms were abnormal in all five cocaine-exposed infants presenting with apnea of infancy and in seven of the remaining 27 asymptomatic cocaine-exposed infants. Apnea density was significantly greater in cocaine-exposed infants. All infants showing an abnormal pneumogram were treated with theophylline, with normalization of the repeat pneumogram two weeks later. No infant died of SIDS on follow-up. As a possible mechanism, the authors suggested that increased circulatory catecholamine levels could depress a hypoxic arousal response. In contrast to these findings, Bauchner et al. found no increased incidence of SIDS in cocaine-exposed infants (1/174, 5.6/1000) compared to controls (4/821, 4.9/1,000), although both incidences were increased over nationwide rates in their low socioeconomic Boston population.[39] Both authors agree that large-scale epidemiologic studies are needed to separate the effect of cocaine itself from other factors, e.g., low socioeconomic status, black race, cigarette smoking, alcohol and polydrug abuse, etc., which may impact on the SIDS rate. It is also important to remember that the links between "abnormal" cardiorespiratory tracings, apnea, and SIDS are still very tenuous.

Environmental hazards. Recent reports indicate that cocaine exposure may occur in young infants after they leave the hospital. Shannon et al. surveyed 1,680 consecutive urines from 1,120 pediatric patients in a children's hospital.[40] Of the total sample, 52 (4.6%) had specimens positive for cocaine or a cocaine metabolite. Three infants, ages one to seven months, were found to have positive cocaine screens after being seen for abnormal neurologic findings[2] or a well baby examination.[1] Subsequently, Bateman and Heagarty described four infants admitted to a New York City municipal hospital with abnormal neurologic findings ascribed to passive "crack" inhalation.[41] Two of the infants presented with seizures and two infants showed abnormal neurologic signs, such as drowsiness and unsteady gait. The authors acknowledge, however, that evidence for the postulated route of cocaine toxicity, passive inhalation of freebase, is circumstantial. In another case report, Rivkin and Gilmore describe a nine-month-old infant who developed refractory seizures, apnea, and cyanosis following reported ingestion of cocaine left over from an adult party the night before.[42] These few case descriptions should be noted in relation to "possible SIDS cases" and the need to rule out environmental toxins before labelling an infant death as SIDS.

Developmental outcome. Much concern has been voiced regarding the ultimate neurobehavioral prognosis of infants following intrauterine exposure to cocaine. Based on risk factors, it appears reasonable to voice these

concerns. Commonly, the parents may be of poor socioeconomic status and culturally deprived. The mother may be poorly nourished, may be at risk for medical and sexually transmitted diseases, including AIDS, and may receive little or no prenatal care. The infants frequently show suboptimal body and head growth during the intrauterine period. Uterine flow may be acutely or chronically compromised due to cocaine-induced vasoconstriction, leading to fetal hypoxia. Central nervous system anomalies may be present. After birth, neurologic and neurobehavioral abnormalities are common. In addition, electroencephalographic and echoencephalographic abnormalities have been well documented. Stimulation for intellectual growth may be lacking because of prolonged hospital stays, infrequent and inappropriate parental contact, placement in a congregate care facility, or discharge to a home in which intellectual nurturing is lacking.

In spite of these valid concerns, follow-up studies of large numbers of "cocaine babies" are presently lacking. The lay press has reported anecdotal experiences with the first cohort of three to five-year-old children born in this "crack" epidemic.[43] Some workers have characterized "cocaine babies" as showing significant deficits in environmental interactions such as play groups and nursery schools.[43] These babies have been described as showing less representational play, decreased fantasy play and curious exploration, and lesser quality of play. Others have described these children as "joyless," unable to fully participate in either structured or unstructured play situations, with attention deficits and flat apathetic moods.[43] As more data are published, we will probably come to view this epidemic of cocaine use as having very serious negative impact on a very large number of America's young children.

AMPHETAMINES

Although amphetamines have been used since the 1930s and were certainly used to some extent during pregnancy, especially during the 1960s and 1970s, only a scanty literature exists describing their effects on the fetus, neonate, and young infant. This may soon change since a smokeable form of methamphetamine, called "ice" or "crystal," is reportedly widely used in Hawaii and has made its recent appearance in the United States.

In addition to its other actions, amphetamine (racemic-B-phenylisopropylamine) has powerful central nervous system stimulant actions. Amphetamine causes increased wakefulness, alertness, mood elevation, elation, and euphoria, similar to cocaine. These effects are caused by stimulation of the release and blocking of reuptake of the neurotransmitters dopamine, norepinephine, or serotonin. Acute neuropsychiatric effects of amphetamine include agita-

tion, tremor, hyperreflexia, irritability, confusion, aggressiveness, and panic states, among others. This is usually followed by fatigue and depression. Addiction and tolerance to amphetamine often occur. Methamphetamine is structurally similar to amphetamine, but has relatively greater central effects and less prominent peripheral actions.

Since cocaine and amphetamines have similar central physiologic effects, their impact on pregnancies should be similar. Both agents cause vasoconstriction and hypertension, which may result in acute or chronic fetal hypoxia. One early experience was reported by Eriksson et al. from Sweden, where intravenous amphetamine use increased dramatically during the 1960s.[44] The authors describe the perinatal course in 23 patients who were chronic amphetamine users, six of whom reportedly stopped amphetamine abuse during the pregnancy. Amphetamine use was associated with reduced prenatal care and an increased incidence of low birth weight babies. Neurologic abnormalities consisted of unexplained seizures in one infant and drowsiness and inabililty to feed in two others. In a later report by Eriksson et al., 69 amphetamine-using women were studied, 52 of whom took amphetamine through the entire pregnancy.[45] Although a concurrent control group was not compared, the authors reported a high perinatal mortality rate, high incidence of obstetric and pregnancy-related complications, an increased number of congenital malformations, and high rate of neonatal neurologic abnormalities in the drug-exposed group.

In a more recent study Oro and Dixon reported on 46 infants born to mothers who took cocaine and/or methamphetamine during the studied pregnancies.[46] The stimulant group included exposure to cocaine,[13] methamphetamine,[28] and cocaine plus methamphetamine.[5] Comparison among the stimulant groups showed no difference in selected perinatal variables; neurologic and physiologic abnormalities in the infants ascribed to the two stimulants were felt to be similar. Use of stimulants led to an increase in placental abruptions and reductions in gestational age, birth weight, length and head circumference compared to controls. After birth, stimulant-exposed infants showed abnormal weight change patterns, losing more weight and subsequently gaining weight more slowly compared to controls. Neurologically, stimulant-exposed infants showed abnormal sleep patterns, tremors, poor feeding, hyperactive reflexes, abnormal cry, and state disorganization, among other abnormalities. The authors note that lethargy and poor feeding followed the hyperirritable stage in some methamphetamine-exposed infants.

Animal studies assessing the impact of prenatal amphetamine administration on neonatal brain physiology and behavior have been summarized by Middaugh.[47] Animal-derived evidence indicates that maternal amphetamine administration reduced norepinephine levels in brains of newborn mice, which might affect neurotransmitter synthesis and function. Behaviorally, prenatal amphetamine administration led to changes in motor activity and reduced performance on specific performance testing in offspring. Animal data, however, have shown inconsistencies that preclude the drawing of firm conclusions. Middaugh feels, however, that theoretical considerations with limited empiric data still suggest that exposure to amphetamine during the gestational period may certainly prejudice long-term neurobehavioral outcome. It should be pointed out, however, that no long-term follow-up studies assessing fetal exposure to amphetamines in humans are yet available.

SOCIETY'S APPROACH TO MATERNAL DRUG USE

Frustration with our nation's inability to deal effectively with our latest cocaine epidemic has created a very punitive mood in dealing with drug-using women.[48] At the present time nine states have instituted criminal action against drug-using women despite those states' inability or reluctance to provide treatment and counseling specifically designed for maternal substance abuse. A punitive rather than rehabilitative approach runs counter to medical and judicial precedent and may drive "hard to reach" women further from the health care system. Failure to provide family-based rehabilitation, when possible, places children in already overburdened and stressed child welfare and foster care systems. Drug-using women, frequently battered and abused as children and adults, need comprehensive medical, obstetric, psychiatric, and drug counseling treatment. Our goals of promoting healthy mothers and children can best be met by provision of such comprehensive services rather than abandoning these unfortunate women in a time of great need.

REFERENCES

1. Musto, D.F.: *The American Disease: Origins of Narcotic Control.* New Haven and London, Yale University Press, 1973, p. 112.
2. Opium Problem, 1910. U.S. Senate, 61st Congress, 2nd Session, Document No. 377. Washington, D.C., Gov. Print. Off., 1910, p. 50.
3. Marriott, M.: After 3 years, crack plague in New York City only gets worse. *The New York Times,* February 20, 1989, p. A:1.
4. Crack: a disaster of historic dimension, still growing (editorial). *The New York Times,* May 28, 1989, p. E14.
5. Labaton, S.: New tactics in the war on

drugs tilt scales of justice off balance. *The New York Times,* December 29, 1989, p. A1.
6. Some war: meanwhile, crack undermines America (editorial), *The New York Times,* September 24, 1989, p. E24.
7. Kerr, P.: Crack and resurgence of syphilis spreading AIDS among the poor. *The New York Times,* August 18, 1989, p. A1.
8. Novick, L.F., Berns, D., Stricof, R., et al.: HIV seroprevalence in newborns in New York State. *J.A.M.A. 261*:1745-50, 1989.
9. Novello, A.C., Wise, P.H., Willoughby, A., et al.: Final report of the United States Department of Health and Human Services Secretary's Work Group on pediatric human immunodeficiency virus infection and disease: content and implications. *Pediatrics 84*:547–55, 1989.
10. *City Health Inform. 8*:4, 1989.
11. The no-parent child (editorial). *The New York Times,* December 24, 1989, p. E10.
12. Kolata, G.: In cities, poor families are dying of crack. *The New York Times,* August 11, 1989, p. A1.
13. Trost, C.: Born to lose. *The Wall Street Journal,* July 18, 1989, p. 1.
14. Califano, J.: Drug war: Fool's errand No. 3. *The New York Times,* December 8, 1989, p. A39.
15. Freudenheim, M.: More aid for addicts on the job. *The New York Times,* November 13, 1989, p. D1.
16. Gross, J.: Cocaine and AIDS in New York add to infant deaths. *The New York Times,* February 18, 1988, p. A1.
17. Mothers, babies and crack (editorial). *The New York Times,* May 14, 1989, p. E22.
18. Chasnoff, I.J.: Drug use and women: establishing a standard of care. *Ann. N.Y. Acad. Sci. 562*:208–10, 1989.
19. Farrar, H.C. and Kearns, G.L.: Cocaine: clinical pharmacology and toxicology. *J. Pediatr. 115*:665–75, 1989.
20. Chasnoff, I.J., Burns, W.J., Schnoll, S.H., et al.: Cocaine use in pregnancy. *N. Engl. J. Med. 313*:666–69, 1985.
21. Hadeed, A.J. and Siegel, S.R.: Maternal cocaine use during pregnancy: effect on the newborn infant. *Pediatrics 84*:205–10, 1989.
22. Bingol, N., Fuchs, M., Diaz, V., et al.: Teratogenicity of cocaine in humans. *J. Pediatr. 110*:93–96, 1987.
23. Chasnoff, I.J., Griffith, D.R., MacGregor, S., et al.: Temporal patterns of cocaine use in pregnancy. *J.A.M.A. 261*:1741–44, 1989.
24. Zuckerman, B., Frank, D., Hingson, R., et al.: Effects of maternal marijuana and cocaine use on fetal growth. *N. Engl. J. Med. 320*:762–68, 1989.
25. Chouteau, M., Namerow, P.B. and Leppert, P.: The effect of cocaine abuse on birth weight and gestational age. *Obstet. Gynecol. 72*:351–54, 1988.
26. Cherukuri, P., Minkoff, H., Feldman, J., et al.: A cohort study of alkaloidal cocaine ("crack") in pregnancy. *Obstet. Gynecol. 72*:147–51, 1988.
27. Fulroth, R., Phillips, B., and Durand, D.J.: Perinatal outcome of infants exposed to cocaine and/or heroin in utero. *Am. J. Dis. Child. 143*:905–10, 1989.
28. Doberczak, T.M., Thornton, J.C., Bernstein, J., et al.: Impact of maternal drug dependency on birth weight and head circumference of offspring. *Am. J. Dis. Child. 141*:1163–67, 1987.
29. Ryan, L., Ehrlich, S., and Finnegan, L.: Cocaine abuse in pregnancy: effects on the fetus and newborn. *Neurotoxicol. Teratol. 9*:295–01, 1987.
30. Chasnoff, I.J., Chisum, G.M., and Kaplan, W.E.: Maternal cocaine use and genitourinary tract malformations. *Teratology 37*:201–04, 1988.
31. Madden, J.D., Payne, T.F., and Miller, S.: Maternal cocaine abuse and effect on the newborn. *Pediatrics 77*:209–11, 1986.
32. Doberczak, T.M., Shanzer, S., Senie, R.T., et al.: Neonatal neurologic and encephalographic effects of intrauterine cocaine exposure. *J. Pediatr. 113*:354–58, 1988.
33. Dixon, S.D. and Bejar, R.: Echoencephalographic findings in neonates associated with maternal cocaine and methamphetamine use: incidence and clinical correlates. *J. Pediatr. 115*:770–78, 1989.

34. Tenorio, G.M., Nazvi, M., Bickers, G.H., et al.: Intrauterine stroke and maternal polydrug abuse. *Clin. Pediatr. 27*:565–67, 1988.
35. Shih, L., Cone-Wesson, B., and Reddix, B.: Effects of maternal cocaine abuse on the neonatal auditory system. *Int. J. Pediatr. Otorhinolaryngol. 15*:245–51, 1988.
36. Chasnoff, I.J., Lewis, D.E., and Squires, L.: Cocaine intoxication in a breast-feeding infant. *Pediatrics 80*:836–38, 1987.
37. Chaney, N.E., Franke, J., and Wadlington, W.B.: Cocaine convulsions in a breast-feeding baby. *J. Pediatr. 112*:134–35, 1988.
38. Chasnoff, I.J., Hunt, C.E., Kletter, R., et al.: Prenatal cocaine exposure is associated with respiratory pattern abnormalities. *Am. J. Dis. Child. 143*:583–87, 1989.
39. Bauchner, H., Zuckerman, B., McClain, M., et al.: Risk of sudden infant death syndrome among infants with in utero exposure to cocaine. *J. Pediatr. 113*:831–34, 1988.
40. Shannon, M., Lacouture, P.G., Roa, J. et al.: Cocaine exposure among children seen at a pediatric hospital. *Pediatrics 83*:337–42, 1989.
41. Bateman, D.A. and Heagarty, M.C.: Passive freebase cocaine ("crack") inhalation by infants and toddlers. *Am. J. Dis. Child. 143*:25–27, 1989.
42. Rivkin, M. and Gilmore, H.E.: Generalized seizures in an infant due to environmentally acquired cocaine. *Pediatrics 84*:1100–02, 1989.
43. Kantrowitz, B.: The crack children. *Newsweek,* February 12, 1990, p. 62–63.
44. Eriksson, M., Larsson, G., Winbladh, B., et al.: The influence of amphetamine addiction on pregnancy and the newborn infant. *Acta Pediatr. Scand. 67*:95–99, 1978.
45. Eriksson, M., Larsson, G., and Zetterstrom, R.: Amphetamine addiction and pregnancy. *Acta Obstet. Gynecol. Scand. 60*:253–59, 1981.
46. Oro, A.S. and Dixon, S.D.: Perinatal cocaine and methamphetamine exposure: maternal and neonatal correlates. *J. Pediatr. 111*:571–78, 1987.
47. Middaugh, L.D.: Prenatal amphetamine effects on behavior: possible mediation by brain monoamines. *Ann. N.Y. Acad. Sci. 562*:308–18, 1989.
48. Chavkin, W., and Kandall, S.R.: Between a "rock" and a hard place: perinatal drug abuse. *Pediatrics 85*:223–25, 1990.